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The overall purpose of this study is to determine the relationship between skeletal and oral bone density, identify factors influencing bone loss, and determine the relationship between osteoporosis and oral bone loss, periodontal disease and tooth loss. We hypothesize that reduction in bone density leading to osteoporosis, plays a significant role in increasing susceptibility to destructive periodontitis and tooth loss. Sensitive and accurate measures of skeletal and oral bone mineral density, periodontal disease and tooth loss will be used. A wide variety of other risk factors for both osteopenia and periodontal disease will be assessed. A total of 1300 subjects are being recruited from an ongoing NIH funded study cohort, the Women's Health Initiative (WHI). Preliminary research findings from our pilot study determined that bone loss in the hip or spine is strongly associated bone loss in the jaw. Also, that bone loss in the hip was associated with tooth loss even when controlling for factors such as age, menopause, estrogen use, body mass and smoking.[1] We have just completed year three of a four year study. Data collection will continue into year-4, as such, findings are not yet available to report.

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Gea Nactawski-Dende 10/12/99

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INTRODUCTION

The overall purpose of this study is to determine the relationship between skeletal and oral bone density, identify factors influencing bone loss, and determine the relationship between osteoporosis and oral bone loss, periodontal disease and tooth loss. We hypothesize that reduction in bone density leading to osteoporosis, plays a significant role in increasing susceptibility to destructive periodontal disease and tooth loss. Sensitive and accurate measures of skeletal and oral bone mineral density, periodontal disease and tooth loss are used in this study. A wide variety of other risk factors for both osteopenia and periodontal disease will be assessed as part of this study. A total of 1300 subjects are being recruited from an ongoing NIH funded study cohort, the Women's Health Initiative (WHI), making this an efficient and cost effective study. A limited number of studies have assessed bone loss in the oral cavity and have suggested that low bone density is associated with severe periodontal disease. However, these studies have been plagued with small sample sizes and poor assessments of confounding factors such as smoking, alcohol intake, and age, among others. Our study will assess these factors in detail. Our preliminary research findings have determined that bone loss in the hip or spine is strongly associated bone loss in the jaw. Also, that bone loss in the hip was associated with tooth loss even when controlling for factors such as age, years since onset of menopause, estrogen use, body mass and cigarette smoking.[1] (A publication which includes these preliminary data is included in the Appendix).

The U.S. population is projected to include an increasing proportion of older men and women in the next few decades, including retired and active military personnel. Hence, management of two of the most common chronic diseases in older persons, osteoporosis and periodontal disease, will demand increasing health service resources. New approaches to prevention, early diagnosis and intervention of these diseases are critical. The proposed study has great practical significance. If oral bone loss is a predictor of low skeletal bone, those people detected on a dental exam to have oral bone loss could be targeted for further evaluation for osteoporosis. Interventions could be started to prevent further bone loss or fracture. Conversely, those with weak skeletal bones may need evaluation for oral bone loss, preventing further loss of bone and subsequent tooth loss. This study potentially provides a new approach to screening for osteoporosis. Last, treatments affective for osteoporosis may prove useful in the prevention and treatment of oral bone and tooth loss.

BODY

This is an ongoing epidemiologic study entitled "Risk Factors for Osteoporosis and Oral Bone Loss in Postmenopausal Women". Data collection is ongoing and will continue through year 4. In year 4 of the project, data analysis will be started and preliminary results will be presented. The body of this report will highlight the methods/assumptions/procedures used for data collection, provide detail on data collection through 09/15/99, and provide specific information regarding tasks proposed in the outline of work.

Experimental Methods, Assumptions and Procedures:

Population to be studied. Subjects for the dental examination and dual-energy x-ray absorptiometry (DXA) are being recruited from the participants in the Women's Health Initiative. The Women's Health Initiative (WHI) is a major research effort to study methods of disease prevention and health promotion among postmenopausal women. It includes a Clinical Trial and Observational Study (OS). Only women enrolled in the OS will be recruited to join this study. The WHI Observational Study (OS) includes postmenopausal women aged 50-79 years at baseline who were unwilling to participate or ineligible for the CT. As part of WHI the women have many baseline measurements, with clinical outcomes determined at annual intervals. The objectives of the OS are to obtain better estimates of the predictive ability of known risk factors for disease, to unearth new risk factors and biomarkers for disease, and to examine the relationship of change in characteristics to prevalent and future disease. In Buffalo, a total of 2248 women have enrolled into the OS. Women agreeing to participate in the Observational Study will be followed for an average of 9 years by the WHI staff. Baseline data collected as part of the OS will be related to putative risk factors and protective factors.

The current study, "Risk Factors for Osteoporosis and Oral Bone Loss", will add a bone density scan and an oral examination to the Buffalo WHI OS protocol, assess the prevalence and severity of osteopenia in this cohort of women, and evaluate osteopenia's role in development of periodontal disease/oral bone loss, and assess risk variables common or unique to each disease.

Subject recruitment. Subjects are being recruited from the WHI Observational Study participants. Women who are enrolled in the WHI Observational Study are contacted by mail and given information about the Osteoporosis/Oral Bone Loss study and asked to participate. A recruitment tool is the offer of a free bone density assessment and dental/oral health examination. Each woman who expresses interest in the study is initially given a brief telephone eligibility screen. Those determined eligible are appointed for a clinical examination.

Of th2 2,248 women enrolled in the WHI OS, 1300 are expected to participate in this study. To date, recruitment into this study has been extremely successful. Details of subject recruitment as of 09/15/99 are presented in "Results and Discussion" section of this report.

Mailing. Women who have already entered the WHI OS study are contacted by mail and asked to call our center if they are interested in learning more about participating. When they call, these women are told about the osteo/dental study, given an opportunity to ask questions, and those who are interested are given a brief eligibility screen.

Eligibility Screen. Information collected on the eligibility screen concern criteria for both DXA and dental assessments. DXA scan exclusion criteria include recent use of contrast agents and known aortic calcification, steroid dependency (use of systemic steroids for the past 6 months), and active cancer or cancer chemotherapy. Criteria for the Periodontal exam are that subjects have at least 6 teeth and have had no periodontal surgery in the last 3 months. Age (50 to 79) and

postmenopausal status have already been met as part of WHI. All eligible women are informed that they will be required to sign an informed consent prior to DXA and dental examinations. If women are determined to be both eligible and interested, they are scheduled for an appointment and sent a study packet by mail. The study packet includes information on temporary exclusion criteria to be aware of (i.e. contrast agents), study questionnaires to be completed at home and brought to the study visit, the consent form to read and review, instructions on what to wear and bring with them, information on premedication (if necessary), and a parking pass for the visit.

Examinations and Testing. At the time of the appointment, a DXA scan is performed by a trained and certified x-ray technician. All subjects accepted into the study receive a measurement of bone mineral density by DXA. The DXA sites will include the lumbar spine, femur and forearm, as well as a determination of whole body composition (fat, lean, mineral content). As part of the oral examination, all subjects receive a complete head and neck and intraoral examination with assessment of periodontal disease by both probing depth and assessment of alveolar crestal height. In addition, mandibular bone density is assessed using a stepwedge radiographic technique.

Before examination begins, participants are required to sign an informed consent form which is reviewed with the participant by a member of the staff. Questions are answered on risks, benefits, voluntary participation and confidentiality.

Questionnaires are self-administered and brought to the visit. At the time of the visit the questionnaires are reviewed by study personnel for completeness and accuracy. Participants can request assistance in completing the questionnaires if needed. Additional information (not collected as part of WHI) on osteoporosis risk factors, oral health history, current medication intake and personal habit history are included in the questionnaires.

The **DXA exam** includes: AP/Lateral Assessment of the Lumbar Spine Density (L1, L2, L3 and L4); Femur Density Assessment (femoral neck, Ward's Triangle, trochanteric region, inter-trochanteric region, and total region); Forearm; and Body Composition Assessment (total body skeletal density, fat and lean).

The **Oral Health Examination** includes examination of the head and neck, and oral mucous membranes. Record of restorative appliances, as well as coronal and root caries, and missing teeth are done. Measurements include: plaque assessment, gingival assessment, calculus index, pocket depth measurement, and clinical attachment level (Florida probe). Oral radiographs include periapical x-rays for alveolar crestal height (ACH), and mandibular basal bone mineral density (MBMD). Radiographs are taken using a standardized techniques and measured using a computer-assisted technique using a method, training and calibration procedure developed by Dr. Hausmann and successfully applied locally. Samples of saliva, plaque and blood are collected and frozen.

Results and Discussion:

Analysis of study data and report of results will not be available until year-4 when data collection is complete. However outlined below is a detailed report of our recruitment experience as of the end of year-3. As of 09/15/99 a total 1823 (227 recent) letters have been sent to WHI OS participants. Of these, 1017 women have completed participation in this study. In addition, 192 women are either scheduled to participate, temporarily ineligible but willing, or willing but needing to reschedule. A total of 114 have been uninterested and 197 ineligible for participation. Based on this success, we should meet or exceed our recruitment goal of 1300 enrollees. Further detail on recruitment is presented below.

Recruitment Summary as of 09/15/99

WHI OS Participants Contacted:

1823 Total letters sent to date (used for percentages below)

Visits Completed, Willing and Eligible:

1017 Visits completed (55% of 1823)
56 Appointments scheduled
89 Temporarily ineligible but interested (i.e. recent contrast agent, out of town)
47 Need to reschedule due to cancellation
1209 Total willing, eligible and likely to participate (66% of 814)

No Contact, Ineligible, Not Interested:

26 No contact/no response
15 Undecided
114 Not interested
35 Deceased
197 Ineligible:
- 112 Edentulous/less than 6 teeth
- 30 Fear of x-rays
- 11 Bilateral hip replacement
- 7 Cancer/Disease
- 20 Report being ill
- 1 Positional vertigo
- 2 Not ambulatory
- 1 In nursing home
- 2 Doctor advised against participation
- 8 Fear of dental exam
- 2 Transportation problems

387 Total ineligible or unwilling (21% of 814)

Recent Letters, no contact to date:

227 Recent letters sent/messages left – no response to date (12% of 1823)

Recommendations In Relation To The Outline Of Work:

The Timeline/Statement of Work from our proposal/funding application is presented below. For each of the tasks, a description of what has been completed and the relation to the timeline are described. In general, tasks have initiated and/or completed within the proposed time frame. When the time frame differs, an explanation is provided.

Proposed Timeline From Application:

Task 1: **Months 1-3+:** Hire personnel, complete training and certification (Nurse mgr, DXA tech, Dental Fellow, clerk, data mgr.)

We have hired, trained and certified a number of staff and key personnel. The personnel who have been employed during year-3 of this grant include:

Staff Name	Position
Jean Wactawski-Wende, PhD	Principal Investigator
Robert Genco, DDS PhD	Co-Investigator
Sara Grossi, DDS MS	Co-Investigator
Ernest Hausmann, DMD PhD	Co-Investigator
Myroslaw Hreshchyshyn, MD+	Co-Investigator
Maurizio Trevisan, MD MS	Co-Investigator
Cheryl Klemenz	Project Manager/Data Manager
Laurie Barrick*	DXA Technician
Dorothy Wright	Secretary/Data Clerk
Sharon Chory	Data Entry
June Markello	Dental Hygienist/Assistant

*Position funded through Gebby Foundation grant.
+Dr. Hreshchyshyn died unexpectedly on 05/25/99.

In addition to the investigators and staff employed on the grant, we have had a number of *in kind* contributions of staff from the University at Buffalo:

Staff Name	Position
Mine Tezal, DDS MS	Dentist/Examiner
Jim Katancik, DDS PhD	Dentist/Examiner
Michael Lynch, DMD	Dentist/Examiner
Jeffrey Rogers, DDS	Dentist/Examiner
Linda Roth	Dental Hygienist/Assistant
Patricia Gill	Dental Hygienist/Assistant
Jan Benedek	Dental Hygienist/Assistant
Steve Lancaster	Dental Hygienist/Assistant
Robert Dunford, MS	Dental Data Manager/Statistician

All staff have been trained to conduct their respective duties and certified. All dental training and certification has by done by Dr. Sara Grossi, study co-investigator. Laurie Barrick is a NYS Licensed X-Ray Technician. She was sent to Hologic to receive manufacturer training and is locally trained and monitored by Drs. Wactawski-Wende. Cheryl Klemenz serves as Project Manager and oversees the daily operation of the study and staff. All investigators are actively involved in the project activities and meet regularly to discuss all aspects of the study. Investigators include Drs. Wactawski-Wende, Genco, Grossi, Hausmann, and Trevisan.

Task 2: **Months 1-3:** Identify OS participants from WHI database
Link study files to WHI OS participant files

The roster of all Observational Study participants from the WHI was extracted and a participant database was created for this study. This database is being used for all study mailings and contacts. It is updated periodically from the WHI roster to insure accuracy of address and other contact information. A separate data file has been completed to enter all clinical and questionnaire information we collect during the study. The data files are separate from the files which include patient identifiers for confidentiality reasons, linked by an study identification number.

Task 3: **Months 2-4:** Finalize study questionnaire; pilot test questionnaire

The questionnaires have been completed and approved for use by both our local IRB and the Army IRB. The questionnaires are completed by all participants. The information included on these questionnaires are supplemental to that already collected as part of WHI.

Task 4: **Months 4-6:** Preparation of initial sample mailing and contact to test contact procedures

Conduct pilot testing of examination procedures on sample of OS participants

Create computerized data files for entry of questionnaires and non-computerized clinical data

As reported in the first annual report, sample mailings were conducted in 80 subjects. This process was very useful in determining timing of appointments and logistics for conducting the study. It was also useful for training and certification of staff. The data entry files have been created and data entry is ongoing. The contact letter, screening questionnaires and consent were approved by the Army Human Use and University at Buffalo IRB.

Task 5: **Months 6**-7: Evaluate and revise procedures based on pilot sample

Procedures were evaluated and some revisions of the original grant were requested and received which have been implemented (i.e. blood, saliva and plaque collection; forearm scan). Procedures were set in year 2 and continue to be implemented.

Task 6: **Months 7-40:** Begin weekly mailings to approximately 70 women

Weekly mailings have begun. As of 09/15/99, a total of 1823 OS participants have been contacted by mail. Details of the results of mailings are presented in "Results and Discussion". Our mailings are ongoing into year-4 of the study.

Task 7: **Months 8-40:** Conduct eligibility screens on interested participants

Obtain informed consent

Conduct DXA/Dental evaluations and have participants complete study questionnaires

Continue quality control procedures throughout study to ensure quality of examiners

In an ongoing fashion we have been completing eligibility screen, scheduling appointments for those interested and eligible, obtaining informed consent, conducting both the DXA and dental examinations, collecting questionnaire information, and continuing quality control of all examining staff. As of 09/15/99 a total of 1017 women have completed participation in the study. Task 7 activities will continue into year-4 of the study.

Task 8: **Months 9-42:** Entry of questionnaire data and verification

Data management of computerized files

Entry and verification of the study data has been ongoing. The computerized files for data entry have been created and are in use. The data from both the DXA scan and Dental exam are directly entered at time of visit and will be merged with questionnaire and WHI data when analysis is started. Back up copies of all data files are kept daily.

Task 9: **Months 40-48:** Begin preliminary data analysis; conduct multivariate analysis

Begin manuscript preparation

Inform participants of initial findings of the study

These activities will be conducted in year 4 of this study

Research Accomplishments:

- Successful enrollment of 1017 study subjects (78% of 1300 planned) to date

Reportable Outcomes:

- Training and participation of dentist-scientists in research design, methods and implementation. The following have participated:

Mine Tezal, DDS MS
Jim Katancik, DDS PhD
Michael Lynch, DMD
Jeffrey Rogers, DDS

  In addition, we plan to train additional dentist-scientists in year 4.
- Mine Tezal is planning to conduct her dissertation on part of this data. She is currently completing her periodontology training and is also enrolled in the PhD program in Epidemiology and Community Health.
- An M.S. project planned for Walter Iwanenco, Master's student in Epidemiology and Community Health.
- Hands-on training for graduate students in study implementation including:
  - Renee Brennan (year 4)
  - Jolie Weiss (year 4)
  - Sara Yonder (year 1)
  - Bridgett McGinness (year 2)
  - Cheryl Klemenz (years 1-4)
- Funding has been applied for to the NIH for the study entitled "Bone Mineral Density as a Predictor of Periodontitis". This study is planned to do a 3 year followup of women enrolled in this study.
- When we were awarded the current study, the Gebbie Foundation provided matching funds to purchase the DXA bone density machine and cover the cost of the DXA technician to prefrom the scans.
- A repository of blood, saliva and plaque has been established. The samples were collected as part of this study. Samples are stored in liquid nitrogen awaiting analysis.
- To date, no manuscripts, abstracts, presentations, patents, licenses, cell lines, or tissues have resulted from this grant.

CONCLUSIONS

Results of this research will not be available until the last year of funding, however the importance and implications of this study are many. The proposed study has great practical significance since if oral bone loss is a predictor of skeletal bone loss, those women who are detected on dental exam to have oral bone loss could be targeted to have further evaluation of skeletal bone density to determine their risk of osteoporosis. These women could then be targeted for interventions which could prevent progression and/or future fracture. Conversely, women with severe skeletal osteopenia may need to be evaluated for risk of oral bone loss, in order to target interventions to prevent progression and subsequent tooth loss. This study potentially provides a new approach for screening for women at risk for osteoporosis.

REFERENCES

1. Wactawski-Wende J, Grossi SG, Trevisan M, Genco RJ, Tezal M, Dunford RG, Ho AW, Hausmann E, and Hreshchyshyn MM. The Role of Osteopenia in Oral Bone Loss and Periodontal Disease. *J Periodontol* 1996; 67:1076-1084.

APPENDIX

1. Manuscript:

Wactawski-Wende J, Grossi SG, Trevisan M, Genco RJ, Tezal M, Dunford RG, Ho AW, Hausmann E, and Hreshchyshyn MM. The Role of Osteopenia in Oral Bone Loss and Periodontal Disease. *J Periodontol* 1996; 67:1076-1084.

The Role of Osteopenia in Oral Bone Loss and Periodontal Disease

Jean Wactawski-Wende,† Sara G. Grossi,‡ Maurizio Trevisan,† Robert J. Genco,‡ Miné Tezal,‡ Robert G. Dunford,‡ Alex W. Ho,‡ Ernest Hausmann,‡ Myroslaw M. Hreshchyshyn**

OSTEOPOROSIS AND PERIODONTITIS ARE DISEASES which affect a large number of women and men, with incidence increasing with advancing age. Osteopenia is a reduction in bone mass due to an imbalance between bone resorption and formation, favoring resorption, resulting in demineralization and leading to osteoporosis. Osteoporosis is a disease characterized by low bone mass and fragility and a consequent increase in fracture risk. Periodontitis is characterized by inflammation of the supporting tissues of the teeth, resulting in resorption of the alveolar bone as well as loss of the soft tissue attachment to the tooth and is a major cause of tooth loss and edentulousness in adults. The relationship of osteopenia to oral bone loss and periodontal disease has been addressed in a limited number of studies. A review of current knowledge regarding this relationship is presented. Interpretation of the literature is complicated by the variety of methods used to assess osteopenia, oral bone mass, and periodontitis, as well as varying definitions of outcomes of interest. Results of a previously unpublished study are presented which suggest that severity of osteopenia is related to loss of alveolar crestal height and tooth loss in post-menopausal women. The literature on the relationship among these disorders is limited and points to the need for additional studies which thoroughly evaluate the influence of potential confounding factors to further define the relationship between low bone mineral density and periodontal disease in larger populations. Clearer understanding of this relationship may aid health care providers in their efforts to detect and prevent osteoporosis and periodontal disease. Increased dialogue among medical and dental professionals will be increasingly important in achieving and maintaining patients' optimal health. *J Periodontol 1996; 67:1076–1084.*

Key Words: Osteoporosis; osteopenia; periodontal diseases; periodontal attachment; tooth loss; alveolar bone loss; bone density.

Osteoporosis and periodontitis are diseases which affect a large number of men and women, with incidence increasing with advancing age. Osteopenia is a reduction in bone mass due to an imbalance between bone resorption and formation, favoring resorption, resulting in demineralization and leading to osteoporosis. Osteoporosis is a disease characterized by low bone mass and fragility and a consequent increase in fracture risk.[1] Fracture risk appears to be influenced by absolute bone mineral density; however, trabecular structure and propensity to fall influence fracture risk as well. Periodontitis is defined as an inflammation of the supporting tissue of the teeth, usually a progressively destructive change leading to a loss of bone and periodontal ligament.[2] Periodontitis is characterized by resorption of the alveolar bone as well as loss of the soft tissue attachment to the tooth and is a major cause of tooth loss and edentulousness in adults.[3] The relationship of osteopenia to oral bone loss and periodontal disease has been addressed in a limited number of studies. Questions remain about the exact role osteoporosis plays in the establishment of periodontal disease. A review of current knowledge regarding these relationships is presented.

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BACKGROUND

Osteopenia; Osteoporosis

Osteoporosis is one of the most important health concerns in the United States. It affects more than 20 million peo-

ple, most of whom are women, and results in nearly 2 million fractures per year. The treatment of osteoporosis was recently estimated to cost $7 billion to $10 billion per year. Combining all fractures, medical care costs, lost activity, and other indirect factors, the costs of osteoporosis are estimated to reach $18 billion yearly.[4]

Osteopenia is characterized by a reduction in bone mass, whereas osteoporosis is the most severe degree of osteopenia which leads to pain, deformity, or fracture. Osteoporosis is a physiological, gender, and age-related condition resulting from bone mineral content loss and structural change in bones. The rate of bone mineral loss is approximately two times greater in women than men. In women, post-menopausal osteoporosis is a heterogeneous disorder which begins after natural or surgical menopause and leads to fractures within 15 to 20 years from the cessation of ovarian function.[1] It is estimated that at least 1.2 fractures occur in the U.S. each year in women over the age of 45. A white woman who lives to age 80 will have a 15% lifetime risk of suffering a hip fracture; by age 90, 33% of women will have a hip fracture.[5] Mortality in women within 1 year of hip fracture is increased by 20% from that of women without hip fracture, and 50% of those suffering may have decreased walking ability.[6-8]

Peak bone mass is reached sometime between the second to third decade of life. From that point forward cortical bone is lost, on average, 0.3% to 0.5% per year. In women, at the time of menopause, the rate of cortical bone loss is 2% to 3% per year for the next 8 to 10 years. Trabecular bone is lost at 4.8% per year in the 5 to 8 years following menopause.[9] Loss of bone mass occurs when there is an imbalance between resorption and formation, favoring resorption.

Periodontal Disease

The etiology of periodontal disease as a bacterial infection is well established. Several subgingival bacteria including *Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Actinobacillus actinomycetemcomitans,* and spirochetes are leading candidates as etiologic agents in periodontal disease.[10] Some form of periodontal disease affects 75% of the population; severe forms affect 14% of adults of all ages and 30% of older adults.[11] The result of infection by these bacterial agents is loss of soft tissue attachment and resorption of alveolar bone, which lead to eventual tooth loss and edentulousness in adults. These factors in turn result in subsequent residual ridge resorption and further loss of oral bone.

Although periodontal disease is thought to be the result of the insult by an infectious agent, the underlying host susceptibility to that agent may play an important role in the prevalence and progression of oral bone loss leading to tooth loss. The relation between periodontitis, osteopenia, and oral bone loss is important and has significant public health impact. Both osteoporosis and periodontal disease are major health problems in the United States, especially in older populations. As the population ages, the impact of osteoporosis and periodontal disease will be more profound. Determination of the relationship between these two diseases, as well as identification of risk factors common and uncommon to these diseases, will be increasingly important in the prevention of morbidity and mortality related to these disorders in older Americans.

Table 1. Risk Factors for Osteoporosis and Periodontal Disease

Osteoporosis	Common Risk Factors	Periodontitis
Female gender	Cigarette smoking	Plaque
Caucasian or Asian race	Nutritional deficiencies	Stress
Heredity	Increasing age	Diabetes
Menopause	Corticosteroid use	Hormone changes
Petite body build	Immune dysfunction	Medical disorders
Amenorrhea		Osteoporosis
High intake caffeine, protein, salt, phosphate		
Low intake calcium, vitamin D		
Excessive alcohol		
Physical inactivity		
Suboptimal peak skeletal mass		
Medical disorders		

RISK FACTORS

Risk Factors for Osteoporosis

Many factors have been identified which contribute to loss of bone mass and are presented in Table 1 (see 12, 13 for review). These include both non-modifiable and modifiable risk factors. Non-modifiable risk factors for osteoporosis include race,[8,14] thin body build,[15] family history of osteoporosis,[12,13] genetics,[16] female gender,[1] history of fracture,[13] and advancing age.[17,18] Modifiable risk factors for osteoporosis include early age at natural or surgical menopause,[19,20] use of medication including corticosteroids, anti-convulsants and excessive thyroid medication,[21-23] eating disorders,[24] calcium deficiency,[25-28] lack of physical activity,[29,30] cigarette smoking (see 31 for a review), excessive use of alcohol or caffeine,[32,33] and suboptimal skeletal development in early adulthood.[34] However, gonadal hormonal-dependent increase in bone resorption and accelerated loss of bone in the first decade after menopause appear to be the main pathogenic factors in women.[35] Estrogen deficiency appears to play a major role in osteopenia and accelerated loss of bone which is supported by the higher prevalence of osteoporosis in women than men[36] and the effect of estrogen replacement therapy on reduction of osteoporotic hip fractures in postmenopausal women (see 37 for review). Body fat[38] and

the role of endogenous estrogen production are also likely to be important in our understanding of osteopenia.

Gruber reviewed evidence[39] providing support for an important relationship between immune cells and bone. Estrogen, vitamin D, parathyroid hormone, calcitonin, interleukin-1 α and β, TNF-α and β, macrophage colony stimulating factor, granulocyte macrophage colony stimulating factor, interferon γ, leukemia inhibitory factor, IL-6, IL-4, and bone morphogenic proteins (e.g., OP-1) appear to play roles in regulating bone remodeling (see 40 for review). However, the exact role and mechanism of action for most of these factors are not clear.

Risk Factors in Periodontal Disease

Systemic disorders have long been considered as secondary factors in periodontal disease, modulating disease initiation and progression. The role of systemic conditions and disorders proposed to play a role in periodontal disease has been reviewed by Genco and Löe.[3] A list of factors known or suspected to influence periodontal disease occurrence and/or severity is presented in Table 1. Factors associated with periodontal disease include increasing age,[11,41,42] occurrence of pathogenic bacterial plaque,[10] immune dysfunction,[39,40,43] nutritional deficiencies,[44] use of steroidal and other medications,[45] gender,[46-48] stress,[49-52] cigarette smoking,[31,46,47,53] genetics,[54-56] and systemic conditions including neutrophil disorders,[57-60] diabetes,[48,61-63] pregnancy and other occurrences of hormonal alteration,[64-67] and osteoporosis.

There are numerous factors which are common for risk of both periodontal disease and osteoporosis. Clear understanding of the influence and mechanism of action for these factors may assist us in better modeling our understanding of these processes. A review of the relationship between osteoporosis, oral bone loss, and periodontal disease is presented below.

STUDIES OF THE RELATIONSHIP BETWEEN OSTEOPOROSIS, ORAL BONE LOSS, AND PERIODONTAL DISEASE

A review of studies which have attempted to define the relationship between osteoporosis, osteopenia, oral bone loss, and periodontitis is presented below. One hypothesis to describe the association among these factors is that osteoporosis results in less crestal alveolar bone per unit volume. This bone of lesser density may be more readily absorbed (more rapid loss of bone height with a given stimulus for resorption provided by periodontal infection).

Interpretation of the literature in this area is complicated by the varying methods used to assess osteoporosis, oral bone loss, and periodontitis, as well as varying definitions of outcomes of interest. A list of abbreviations for terminology used in this review is presented in Table 2. Methods to assess degree of osteopenia or osteoporosis include various measures of bone density (i.e., SPA, DPA, DXA, QCT, DSR) and/or clinical observations (i.e., fracture). Methods to assess degree of periodontitis include various oral measurements (i.e., ACH, CAL, RRR) and/or clinical outcomes (i.e., tooth loss, bleeding, edentulousness). In addition, demographic makeup of the population under study and control of other risk variables differ markedly across studies. All these factors make interpretation and conclusion based on published reports extremely challenging.

Table 2. List of Abbreviations

ACH	Alveolar Crest Height
CAL	Clinical Attachment Loss
BMC	Bone Mineral Content
BMD	Bone Mineral Density
DPA	Dual Photon Absorptiometry
DSR	Digital Subtraction Radiography
DXA	Dual Energy X-Ray Absorptiometry
QCT	Quantitative Computerized Tomography
RRR	Residual Ridge Resorption
SPA	Single Photon Absorptiometry

Osteoporosis and Oral Bone Loss

Systemic loss of bone density leading to osteoporosis has long been suspected as a systemic risk factor for loss of oral bone, including loss of the alveolar process associated with periodontal infection. Recently from an assessment of osteoporosis in the jaws by dual photon absorptiometry,[68-70] it was found that reduction in total skeletal mass is directly related to reduction in mandibular bone density in women with osteoporosis.[71] It was also shown that post-menopausal women, as well as those with chronic renal failure, often show thinning of the mandibular angular cortex in the region of the gonion.[72] Kribbs et al. showed that mandibular bone mass was significantly correlated with skeletal bone mass in a population of normal women.[73] They further showed that mandibular mass was correlated with all skeletal measures in osteoporotic women and that the height of the edentulous ridge correlated with total body calcium and mandibular mass.[74] Earlier studies by Kribbs and Chesnut[75] and Henrikson and Wallenius[76] showed that the mandible measurements did correlate with skeletal measures of bone mass. However, Mohajery and Brooks[77] found that there was no correlation between skeletal and mandibular bone measurements. Their assessment of skeletal bone mass was made by dual photon absorptiometry for the lumbar spine and femoral neck, while they made mandibular bone density measurements on panoramic and periapical radiographs. It is likely these techniques are not truly comparable; this may explain why Mohajery and Brooks did not find correlations between mandibular bone mass and skeletal mass that others have found.

A study by Humphries and coworkers[78] showed that loss of bone mineral density (BMD) with age in edentulous adult mandibles was significant in females but not in

males. These results suggest that in males, the effect of age was cumulative loss, whereas in females a second factor may be involved—namely, the effect of bone loss associated with menopausal cessation of ovarian function. Studies by Ortman et al.[79] found a statistically significantly higher percentage of women with severe alveolar ridge resorption than men. Recently, Hirai et al.[80] found that the presence of skeletal osteoporosis strongly affects the reduction of the residual ridge in edentulous patients.

Klemetti and coworkers conducted a number of studies on the relationship between indicators of osteoporosis and oral bone loss as part of a larger study on risk factors and prevention of osteoporosis in Finland. These investigators studied the height of the residual ridge and the BMD of the trabecular bone of the mandible assessed by QCT in 74 of 355 menopausal women. They compared mandibular BMD to BMD of the lumbar spine and femur which was measured by DXA. Their study showed that the BMD of the spine and femur correlated well with each other, but not to the BMD of the trabecular bone of the mandible. Residual ridge height did not correlate strongly with any BMD values.[81] In another report, Klemetti studied all 355 edentulous post-menopausal women and determined number of teeth, time of last extraction, and height of alveolar ridges. Time of tooth loss and number of teeth were not correlated with generalized bone density, but clinical height was related to bone density in some regions.[82]

A subsequent study reported on alveolar crest height, duration of edentulousness, and BMD in five different regions of the mandible in 77 post-menopausal women. This study showed that after tooth loss, BMD of the trabecular, but not cortical, regions of the mandible was lower. The authors postulate the mechanism to be the mechanical stress caused by the remaining natural teeth rather than the damage following use of maxillary dentures.[83] They also considered time since last tooth loss in four cortical regions within this cohort of 77 partially or totally edentate post-menopausal women. Density of the cortical bone on the lingual and buccal sides, and distal from the mental foramen, was significantly higher among those who had been edentate 12 to 23 years, but not in those edentate less than 12 or over 23 years compared to dentate subjects. The authors suggest that muscular activity during different phases of edentulousness regulates the bone density in those attachment regions.[84]

Many, but not all, studies have shown a relation between skeletal density and oral bone density, crestal height, or RRR. Factors which influence interpretation of the data include underlying population studied and method of determining oral bone loss or density. The populations studied vary on important characteristics such as prevalence of edentulousness, gender, and underlying prevalence of severe osteopenia. These factors play a role in determining the relation between osteopenia and oral bone loss. Methods for determining oral bone loss are key in describing the relationship between oral bone loss and osteopenia.

Studies Evaluating Methodology to Assess Oral Bone Loss

Several studies have attempted to determine the accuracy and precision of various methods to assess mandibular BMD. Taguchi et al. studied the effect of size and shape of the region of interest on the precision of the measurements of bone mineral content of mandibular bone using QCT. Both dry mandible and a series of calcium carbonate rods were used in this study. The precision of measurements of the region of interest for sizes less than 1 cm^2 was low, but was satisfactory for regions greater than 1 cm^2, making size of region critical. In this study, shape had no influence on precision.[85]

Benson and coworkers studied radiomorphometric index of mandibular cortical bone mass, using the panoramic mandibular index (PMI), in 353 adult subjects. The study cohort was divided equally by sex, age, and race. Blacks were found to have a greater mean PMI than either Hispanic or white subjects, who were statistically similar to each other. Age-related changes comparing younger and older age groups within each gender and racial group indicated a significant decrease in mean PMI with increasing age in both black and Hispanic women. The mean PMI in white men increased with advancing age.[86]

Klemetti et al. studied whether the panoramic mandibular index correlated with BMD determined by DXA of the femoral neck and lumbar spine, or the BMD determined by QCT for trabecular and cortical regions of the mandible. Weak linear correlation of the panoramic mandibular indices with all BMD measurements was seen, with low and high index subgroup means clearly related to bone mineral density.[87] In addition, this group then studied the diagnostic efficacies of three panoramic-based indices compared to bone mineral density by DXA and determined that panoramic dental radiographs were not useful in assessing osteoporosis status.[88]

Hildebolt and coworkers studied the relationship between skeletal DXA and bitewing radiographs. This study suggested that bitewing radiographs were able to detect a 5% or greater change in alveolar BMC and that alveolar BMC could reflect post-cranial BMC. However, results of this study were based on a small sample and need to be reproduced.[89]

Ulm, Solar and others studied 25 edentulous anatomical mandible specimens. BMC was measured by DPA; a significant difference ($P = 0.05$) in BMC was found between men and women.. BMC of male mandibles increased slightly with advancing age while BMC of the female mandible decreased with increasing age.[90,91]

Zubery et al. studied a computer-based qualitative and quantitative radiographic evaluation system based on the

CADIA algorithm. The reproducibility was high, both for the radiographic technique and repeated measurements, with the system able to detect density changes of 0.27 mm of compact bone equivalent. The authors suggest that this system might be capable of quantitatively evaluating small density changes on sequential radiographs for early detection of both caries and periodontal disease.[92]

Devlin and Horner conducted a study to determine whether bone mineral content could be estimated densitometrically in vitro using dental panoramic tomograms (DPT) and a nickel stepwedge. The technique was able to detect differences in four mandibles studied.[93] This technique was then used in vivo to study mandibular osteoporosis in 99 elderly, edentulous individuals. Twenty-seven of the patients exhibited osteoporosis according to this DPT measurement. There was a significant difference in the quantitative, densitometrically derived measurements of mandibular bone density between the osteoporotic and non-osteoporotic groups and between males and females.[94]

Jeffcoat and Reddy have developed a technique using digital subtraction radiography and a calibrated reference wedge to assess peri-implant bone change over time. This technique was tested and produced excellent correlation between the actual and calculated lesion mass. This methodology is promising in its potential application in assessing oral bone density at baseline and bone density changes over time.[95]

Corten et al. measured BMD of the mandible using DXA in patients with and without teeth. The reproducibility was determined by the coefficient of variation. For ex vivo measurements, the coefficient of variation was 0.5%, and for in vivo measurements it was 3.0%. This method to assess mandibular BMD allows determination of an average BMD in the mandible. This mandibular measurement is then able to be directly compared to measurements in the axial skeleton using the method of density determination. The dose received per mandible scan was relatively low, equaling that of one bitewing/radiograph.[96]

Methodologies to assess BMD in the oral cavity continue to be assessed and are improving. Many of the technologies for assessing oral bone mass are useful in a research setting but are not applicable at this time for wide use in the community, either because of lack of testing in the general community or lack of availability of the instrumentation. Technology to assess oral bone mass will need to be refined before it is useful in the general clinical setting.

Osteoporosis and Tooth Loss

Krall and others studied tooth loss and skeletal bone density in 329 post-menopausal women who were participating in a study of calcium supplementation. Number of natural teeth remaining were compared to BMD of the lumbar spine (DPA) and radius (SPA) at baseline, prior to randomization to the calcium trial. The BMD of both the spine and the radius correlated well with number of remaining teeth. In those women with full dentures, BMD of the spine (and possibly the hip and radius) was correlated with age at which full dentures were received. Increasing age, increasing packyears of cigarette smoking, and decreasing years of education were statistically correlated with tooth loss and denture use.[97]

The contributions of osteoporosis to tooth loss were evaluated by Daniell in 208 women, aged 60 to 69, who had either upper or lower full dentures. The smoking habits of the women and their current osteoporosis severity (estimated by percent cortical area at the metacarpal midshaft) were compared. He found a strong association between smoking and edentulousness.[98] This study was essentially an uncontrolled case study and, although it strongly points to a role for osteoporosis and smoking in edentulousness, it does not prove a relationship between these factors and the reason for edentulousness, which was presumed to be periodontal disease.

Lundgren and Rosenquist studied disuse osteopenia in rats following extraction or following extraction plus calcium deficiency. Both disuse and calcium deficiency caused osteopenia. This induced osteopenia did not seem to impair the healing process after tooth extraction in the short term, but the alveolar height at the extraction site was higher in the experimental group than in the control group 4 weeks after extraction.[99]

Tooth loss has been observed to be related to bone density in the oral cavity in a limited number of studies. When interpreting results in various regions, it is necessary to remember that tooth loss is highly influenced not only by periodontal disease, but also by local practices of the dental community as well as other factors related to oral health.

Osteoporosis and Periodontal Disease

Several studies have attempted to show a relationship between periodontal disease and metacarpal bone index.[100,101] However, the metacarpal index may not give a correct estimate of the bone mineral content of the jaws.[102] Recently von Wowern et al.,[68] in a case-control study comparing 12 female patients with osteoporotic fractures and 14 normal women, found that there was significantly greater periodontal attachment loss in the osteoporotic women than in the normal women. It was interesting, however, that in both groups the bone mineral content values measured by DPA were significantly lower than the normal reference value for young women, suggesting that generalized osteopenia occurred in the control group as well. Reduced bone density seen in the osteoporosis group was clinically associated with fractures.

von Wowern and Hjorting-Hansen studied mandibular BMC in relation to vestibulolingual sulcoplasty and found

a significant negative relationship between the initial BMC values and the BMC percentage loss in the denture-wearing sites in both young and elderly, and a significant positive relationship between the BMC percentage loss in two sites of the mandible in the elder group. The rate of residual ridge reduction could be predicted from the initial mandibular BMC value and seemed to be dependent on the age-related mandibular BMC loss.[103]

Elders and coworkers performed oral exams, assessed alveolar bone height by bitewing radiographs, and assessed spinal BMD and metacarpal cortical thickness (MCT) in 286 women aged 46 to 55. Sixty (21%) of the cohort were edentulous. Compared to the dentate subjects, the lumbar BMD and MCT of the edentulous women were not significantly different. In the dentate subjects, no significant correlation was observed between the clinical parameters of periodontitis (mean probing depth, bleeding after probing, and number of missing teeth) and BMD/MCT, nor between BMD and alveolar bone height. The authors concluded from their study that systemic bone mass may not be an important factor in the pathogenesis of periodontitis,[104] although the design of this study may have precluded determination of a positive association.

In another study of the effects of osteoporosis on periodontal disease, Groen et al.[105] found toothlessness and severe periodontal disease among 38 patients, aged 43 to 73, who exhibited clinical and radiographic signs of osteoporosis. The author noted poor oral hygiene with large calculus deposits in many of the patients, but the study had no control group and hence is difficult to interpret.

Kribbs[106] found that patients in an osteoporotic group had less mandibular bone and a thinner cortex at the gonion than a comparable non-osteoporotic group. The osteoporotic population had lost 6.9 mandibular teeth, and the normal population had lost 4.5 mandibular teeth—a statistically significant difference ($P < 0.05$). However, there were no differences between the osteoporotic and non-osteoporotic group in mean probing depth or recession from the cementoenamel junction plus probing depth, which is a measurement of periodontal probing attachment loss. Since plaque, calculus, smoking habits, reason for tooth extraction, and other confounding factors were not assessed in this population, the findings are difficult to interpret concerning the role of osteoporosis in periodontal disease.

In summary, studies have indicated that the strongest associations with osteopenia and periodontitis are for associations between BMD and measures of loss of oral bone (ACH, RRR), and with tooth loss. Studies linking attachment loss or probing depth have not shown consistent relationships across studies; however, the number of studies is limited. Results of one additional study are presented below.

Osteopenia and Periodontitis in Post-Menopausal Women in Western New York

The relationship between osteopenia and periodontal disease was studied in a cohort of 70 post-menopausal white women aged 51 to 78 (63.05 ± 6.73; mean ± S.D.) in Buffalo, New York. Women were recruited as volunteers through the Periodontal Disease Research Center or the Gynecology Osteoporosis Research Center at the University at Buffalo. This study was designed to include subjects exhibiting established periodontitis, defined as having 6 mm or more interproximal CAL and at least one site with probing depth of 5 mm or greater, and approximately equal numbers of those with low levels of CAL.[107] Exclusion criteria for acceptance into the study were: onset of menopause before age 40; history of parathyroid disease or any other metabolic disease affecting bone; current or long-term use of steroid medication; or less than seven natural teeth present in the lower arch. Complete dental and bone density assessments were performed, and a comprehensive medical and dental history was taken. Periodontal disease was determined using both clinical attachment level (measured by a Florida probe) and interproximal alveolar crest height (ACH), using the method by Hausmann and others.[108] In addition, the number of remaining teeth was recorded at the time of oral examination. Bone mineral density was assessed by using dual-energy X-ray absorptiometry.[§] Skeletal bones assessed included the lumbar spine and femur. Specific regions of interest were the anterior-posterior lumbar spine (AP-L2) and five regions of the femur (trochanter, inter-trochanter, Ward's triangle, femoral neck, and total femur).

For the women in this study the mean CAL was 2.8 ± 1.1 mm, ranging from 1.4 mm to 6.7 mm, with 24 (40%) having established periodontitis. The mean ACH was 3.1 ± 1.0 mm, ranging from 1.3 mm to 5.8 mm, and the mean number of lost teeth was 5.3 ± 5.7. The association between the BMD measurements and periodontal measurements was assessed by partial correlations. These correlations were obtained from multiple linear regression models that are used in a stepwise regression technique. The correlations represent the additional contribution towards predicting the development of periodontal disease after adjusting for the contributions of the other independent variables that have been shown to be predictors of disease level or osteopenia. These variables included age, years since menopause, estrogen use, body mass index, and smoking level. The resulting partial correlations are presented in Table 3. There was a positive correlation between mean ACH and BMD of the AP spine ($R = 0.24$; $P = 0.057$), trochanter ($R = 0.28$; $P = 0.028$), Ward's triangle ($R = 0.26$; $P = 0.037$), and total femur ($R = 0.26$; $P = 0.040$). The relationship between CAL and

[§]QDR-2000, Hologic, Inc., Waltham, MA.

Table 3. Correlation Between Measures of Periodontal Disease and Osteopenia in Post-Menopausal Women*

	CAL		ACH		# Teeth	
	Corr.	*P*-Value	Corr	*P*-Value	Corr	*P*-Value
Spine						
L2 (AP)	.19	.1228	.24	.0568	.15	.2294
Femur						
Trochanter	.17	.1809	.28	.0275	.15	.2264
Inter-trochanter	.13	.3180	.21	.0915	.23	.0678
Ward's triangle	.16	.2131	.26	.0371	.31	.0127
Femoral neck	.15	.2369	.21	.1001	.13	.3073
Total femur	.16	.2090	.26	.0401	.21	.0933

*Correlations adjusted for age, years since menopause, estrogen use, body mass index, and smoking (packyears). N = 70 subjects.
CAL = Clinical Attachment Level; ACH = Alveolar Crest Height; # Teeth = Number of remaining teeth.

BMD did not reach statistical significance for any areas of the spine or femur. Number of remaining teeth was significantly correlated with Ward's triangle (R = 0.31; *P* = 0.013). Conclusions from this study were that osteopenia is related to ACH and tooth loss in post-menopausal women. The correlation coefficients from our study were similar to those reported in previous studies. Measures of alveolar crest height correlated better with measures of bone mineral density at all skeletal sites measured than did attachment loss. Additional studies are needed to define the relationship between bone mineral density and periodontal disease while evaluating further the influence of possible confounding factors for osteopenia and periodontal disease in larger cohorts of women.

SUMMARY

A number of studies have been presented and have generally suggested that osteopenia does play a role in the establishment of periodontal disease. Periodontal disease is characterized by resorption of the alveolar bone as well as loss of the soft tissue attachment to the tooth. The etiology of periodontal disease as a bacterial infection is well established; however, loss of oral bone as a result of osteopenia is probably important in the creation of a susceptible host. In addition, periodontitis and osteopenia may share common etiologic agents which may either directly influence or modulate both disease processes. Many of the studies conducted to date suggest there is a relationship between these diseases, but these studies have been plagued by relatively small sample sizes and lack of adequate control of potential confounding variables such as gender, hormone intake, smoking, race, age, stress and distress, diet, body mass, and exercise,[2] among others. Further study of the relationship between osteoporosis, oral bone loss, and periodontal disease is needed. Clearer understanding of this relationship may aid health care providers in their efforts to detect both of these diseases earlier. In addition, preventive strategies may be developed which impact incidence of both diseases. Increased dialogue among medical and dental professionals will be increasingly important in achieving and maintaining optimal health of patients.

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REFERENCES

1. National Institutes of Health. Consensus Development Conference. *JAMA* 1984;252:799–802.
2. American Academy of Periodontology. *Glossary of Periodontal Terms.* 3rd ed. Chicago: The American Academy of Periodontology; 1992.
3. Genco RJ, Löe H. The role of systemic conditions and disorders in periodontal disease. *Periodontol 2000* 1993;2:98–116.
4. Holbrook TL, Grazier K, Kelsey JL, Stauffer RN. The frequency of occurrence, impact and cost of selected musculoskeletal conditions in the United States. Chicago: American Academy of Orthopaedic Surgeons; 1984.
5. Nickens HW. A review of factors affecting the occurrence and outcome of hip fracture, with special reference to psychosocial issues. *J Am Geriatr Soc* 1983;31:166–177.
6. Miller CW. Survival and ambulation following hip fracture. *Bone Joint Surg* 1978;60:930–934.
7. Jacobsen SJ, Goldberg J, Miles TP, et al. Hip fracture incidence among the old and very old: A population-based study of 745,435 cases. *Am J Public Health* 1990;80:871–873.
8. Farmer ME, White LR, Brody JA, et al. Race and sex differences in hip fracture incidence. *Am J Public Health* 1984;74:1374–1380.
9. Kaplan FS. Osteoporosis. Pathophysiology and prevention. *Clin Symp* 1987;39:1–32.
10. Socransky SS, Haffajee AD. Microbial risk factors for destructive periodontal disease. In: Bader JD, ed. *Risk Assessment in Dentistry.* Chapel Hill, NC: University of North Carolina Dental Ecology; 1990:79–90.
11. Miller AJ, Brunelle JA, Carlos JP, Brown LJ, Löe H. *Oral Health of United States Adults. The National Survey of Oral Health in U.S. Employed Adults and Seniors: 1985–1986. National Findings.* Bethesda, MD: U.S. Department of Health and Human Services; 1987. NIH Publication No. 87-2868.
12. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev* 1985;7:178–208.
13. Nevitt MC. Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 1994;20:535–559.
14. Nelson DA, Feingold M, Bolin F, Parfitt AM. Principal components analysis of regional bone density in black and white women: Relationship to body size and composition. *Am J Phys Anthropol* 1991;86:507–514.
15. Edelstein SL, Barrett-Connor E. Relation between body size and bone mineral density in elderly men and women. *Am J Epidemiol* 1993;138(3):160–169.
16. Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. *Nature* 1994;367:284–287.
17. Riggs BL, Wahner HW, Dunn WL, et al. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. *J Clin Invest* 1981;67:328–335.
18. Richelson LS, Wahner HW, Melton LJ, et al. Relative contributions of aging and estrogen deficiency to postmenopausal bone loss. *N Engl J Med* 1984;311:1273–1275.
19. Hreshchyshyn MM, Hopkins A, Zylstra S, Anbar M. Effects of

natural menopause, hysterectomy and oophorectomy on lumbar spine and femoral neck bone densities. *Obstet Gynecol* 1988;72: 631–638.
20. Kreiger N, Kelsey JL, Helford TR, et al. An epidemiologic study of hip fracture in postmenopausal women. *Am J Epidemiol* 1982;116:141–148.
21. Reid IR. Steroid osteoporosis. *Osteoporos Int* 1993;3(suppl 1): 144–146.
22. Jones G, Sambrook PN. Drug-induced disorders of bone metabolism. Incidence, management and avoidance. *Drug Saf* 1994;10: 480–489.
23. Duncan WE, Chang A, Solomon B, Wartofsky L. Influence of clinical characteristics and parameters associated with thyroid hormone therapy on the bone mineral density of women treated with thyroid hormone. *Thyroid* 1991;1:183–190.
24. Putukian M. The female triad. Eating disorders, amenorrhea, and osteoporosis. *Med Clin North Am* 1994;78:345–356.
25. Tilyard MW, Spears GRS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with Calcitriol or calcium. *New Engl J Med* 1992;326:359–366.
26. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. *New Engl J Med* 1991;325:1191–1195.
27. Chesnut CH. Osteoporosis and its treatment. *New Engl J Med* 1992;326:406–407.
28. Haddad JG. Vitamin D - solar rays, the Milky Way or both? *New Engl J Med* 1992;326:1213–1215.
29. Zylstra S, Hopkins A, Erk M, Hreshchyshyn M, Anbar M. Effect of physical activity on lumbar spine and femoral neck bone densities. *Int J Sports Med* 1989;10:181–186.
30. Kannel WB, Sorlie P. Some health benefits of physical activity, The Framingham Study. *Arch Intern Med* 1979;139:857–861.
31. Johnston JD. Smokers have less dense bones and fewer teeth. *J Royal Soc Health* 1994;114:265–269.
32. Barrett-Connor E, Chang JC, Edelstein SL. Coffee-associated osteoporosis offset by daily milk consumption - The Rancho-Bernardo Study. *JAMA* 1994;271:280–283.
33. Moniz C. Alcohol and bone. *Br Med Bull* 1994;50:67–75.
34. Ortlani S, Trevisan C, Bianchi ML, Gandolini G, Cherubini R, Polli EE. Influence of body parameters on female peak bone mass and bone loss. *Osteoporos Int* 1993;3(suppl 1):61–66.
35. Riggs BL, Melton LJ. Evidence for two distinct syndromes of involutional osteoporosis. *Am J Med* 1986;75:899–901.
36. Nilas L, Christiansen C. Bone mass and its relationship to age and menopause. *J Clin Endocrinol Metab* 1987;65:697–702.
37. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–1037.
38. Daniell HW. Osteoporosis of the slender smoker: Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. *Arch Intern Med* 1976;136:298–304.
39. Gruber HE. Bone and the immune system. *Proc Soc Exp Biol Med* 1991;197:219–225. Review.
40. Pacifici R. Is there a causal role for IL-1 in postmenopausal bone loss? *Calcif Tissue Int* 1992;50:295–299. Editorial.
41. Schei O, Waerhaug J, Lovdal A, Arno A. Alveolar bone loss as related to oral hygiene and age. *J Periodontol* 1959;30:7–16.
42. Abdellatif HM, Burt BA. An epidemiological investigation into the relative importance of age and oral hygiene status as determinants of periodontitis. *J Dent Res* 1987;66:13–18.
43. Masada MP, Person R, Kenney JS, et al. Measurement of interleukin-1a and -113 in gingival crevicular fluid: Implications for the pathogenesis of periodontal disease. *J Periodont Res* 1990;25:156–163.
44. Mehta FS. Prevalence of periodontal disease. 5. Epidemiology in an Indian child population in relation to their socio-economic status. *Int Dent J* 1956;6:31–40.
45. von Wowern N, Klausen B, Olgaard K. Steroid-induced mandibular bone loss in relation to marginal periodontal changes. *J Clin Periodontol* 1992;19:182–186.
46. Grossi SG, Zambon JJ, Ho AW, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *J Periodontol* 1994;65:260–267.
47. Beck JD, Koch GG, Rozier RG, Tudor GE. Prevalence and risk indicators for periodontal attachment loss in a population of older community-dwelling blacks and whites. *J Periodontol* 1990;61: 521–528.
48. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin dependent diabetes mellitus. *J Periodontol* 1991;62:123–130.
49. Baker EG, Grook GH, Schwabacher ED. Personality correlates of periodontal disease. *J Dent Res* 1961;40:396–403.
50. Davis CH, Jenkins CD. Mental stress and oral disease. *J Dent Res* 1962;41:1045–1049.
51. Goldhaber P, Giddon DB. Acute necrotizing ulcerative gingivitis: A study of some of the contributing factors and their validity in an Army population. *Int Dent J* 1964;14:346–358.
52. Shannon IL, Kilgore WG, O'Leary TJ. Stress as a predisposing factor in necrotizing ulcerative gingivitis. *J Periodontol* 1969;40: 240–242.
53. Grossi SG, Genco RJ, Machtei EE, et al. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol* 1995;66:23–29.
54. Hart TC, Marazita ML, Schenkein HA, Diehl SR. Re-interpretation of the evidence for X-linked dominant inheritance of juvenile periodontitis. *J Periodontol* 1992;63:745–749.
55. Michalowicz BS, Aeppli DP, Kuba RK, et al. A twin study of genetic variation in proportional radiographic alveolar bone height. *J Dent Res* 1991;70:1431–1435.
56. Michalowicz BS, Aeppli D, Virag JG, et al. Periodontal findings in adult twins. *J Periodontol* 1991;62:293–299.
57. Bauer WH. The supporting tissues of the tooth in acute secondary agranulocytosis (Arsphenamin neutropenia). *J Dent Res* 1946;25: 501–508.
58. Cohen DW, Morris AL. Periodontal manifestation of cyclic neutropenia. *J Periodontol* 1961;32:159–168.
59. Tempel TR, Kimball HR, Kakehashi S, Amen CR. Host factors in periodontal disease: Periodontal manifestations of Chediak-Higashi syndrome. *J Periodont Res* 1972;7(suppl):26–27.
60. Hamilton RE, Giansanti JS. Chediak-Higashi syndrome: Report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol* 1974;37:754–761.
61. Sandler HC, Stahl SS. Prevalence of periodontal disease in a hospitalized population. *J Dent Res* 1960;39:439–449.
62. Sandler HC, Stahl SS. The influence of generalized diseases on clinical manifestations of periodontal disease. *J Am Dent Assoc* 1954;49:656–667.
63. Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes mellitus and periodontal disease. *J Am Dent Assoc* 1990;121:532–536.
64. Ziskin DE, Blackberg SN, Stout AP. The gingivae during pregnancy. An experimental study and a histopathological interpretation. *Surg Gynecol Obstet* 1933;57:719–726.
65. Maier AW, Orban B. Gingivitis in pregnancy. *Oral Surg Oral Med Oral Pathol* 1949;2:334–373.
66. Ringsdorf WM, Powell BJ, Knight LA, Cheraskin E. Periodontal status and pregnancy. *Am J Gynecol* 1962;83:258–263.
67. Norderyd OM, Grossi SG, Machtei EE, et al. Periodontal status of women taking postmenopausal estrogen supplementation. *J Periodontol* 1993;64:957–962.

68. von Wowern N, Klausen B, Kollerup G. Osteoporosis: A risk factor in periodontal disease. *J Periodontol* 1994;65:1134–1138.
69. von Wowern N. Dual-photon absorptiometry of mandibles: In vitro test of a new method. *Scand J Dent Res* 1985;93:169–177.
70. von Wowern N. Bone mineral content of mandibles: Normal reference values - rate of age related bone loss. *Calcif Tissue Int* 1988;43:193–198.
71. Kribbs PJ, Chesnut CH, Smith DE. Oral findings in osteoporosis. II. Relationship between residual ridge and alveolar bone resorption in generalized skeletal osteopenia. *J Prosthet Dent* 1983;50: 719–724.
72. Bras J, van Ooij CP, Abraham-Inpijn L, Wilmink JF, Kusen GJ. Radiographic interpretation of the mandibular angular cortex: A diagnostic tool in metabolic bone loss. II. Renal osteodystrophy. *J Oral Surg* 1982;53:647–650.
73. Kribbs PJ, Chesnut CH, Ott SM, Kilcoyne RF. Relationships between mandibular and skeletal bone in a population of normal women. *J Prosthet Dent* 1990;63:86–89.
74. Kribbs PJ, Chesnut CH, Ott SM, Kilcoyne RF. Relationships between mandibular and skeletal bone in an osteoporotic population. *J Prosthet Dent* 1989;62:703–707.
75. Kribbs PJ, Chesnut CH. Osteoporosis and dental osteopenia in the elderly. *Gerodontology* 1984;3:101–106.
76. Henrikson PA, Wallenius K. The mandible and osteoporosis. A qualitative comparison between the mandible and the radius. *J Oral Rehabil* 1974;1:67–74.
77. Mohajery M, Brooks SL. Oral radiographs in the detection of early signs of osteoporosis. *Oral Surg Oral Med Oral Pathol* 1992;73: 112–117.
78. Humphries S, Devlin H, Worthington H. A radiographic investigation into bone resorption of mandibular alveolar bone in elderly edentulous adults. *J Dent* 1989;17:94–96.
79. Ortman LF, Hausmann E, Dunford RG. Skeletal osteopenia and residual ridge resorption. *J Prosthet Dent* 1989;61:321–325.
80. Hirai T, Ishijima T, Hashikawa Y, Yajima T. Osteoporosis and reduction of residual ridge in edentulous patients. *J Prosthet Dent* 1993;69:49–56.
81. Klemetti E, Vainio P, Lassila V, Alhava E. Trabecular bone mineral density of mandible and alveolar height in postmenopausal women. *Scand J Dent Res* 1993;101:166–170.
82. Klemetti E, Vainio P. Effect of bone mineral density in skeleton and mandible on extraction of teeth and clinical alveolar height. *J Prosthet Dent* 1993;70:21–25.
83. Klemetti E, Vainio P. Effect of maxillary edentulousness on mandibular residual ridges. *Scand J Dent Res* 1994;102:309–312.
84. Klemetti E, Vainio P, Lassila V. Mineral density in the mandibles of partially and totally edentate postmenopausal women. *Scand J Dent Res* 1994;102:64–67.
85. Taguchi A, Tanimoto K, Ogawa M, Sunayashiki T, Wada T. Effect of size of region of interest on precision of bone mineral measurements of the mandible by quantitative computed tomography. *Dento Maxillofac Radiol* 1991;20:25–29.
86. Benson BW, Prihoda TJ, Glass BJ. Variations in adult cortical bone mass as measured by a panoramic mandibular index. *Oral Surg Oral Med Oral Pathol* 1991;71:349–356.
87. Klemetti E, Kolmakov S, Heiskanen P, Vainio P, Lassila V. Panoramic mandibular index and bone mineral densities in postmenopausal women. *Oral Surg Oral Med Oral Pathol* 1993;75:774–779.
88. Klemetti E, Kolmakov S, Kroger H. Pantomography in assessment of the osteoporosis risk group. *Scand J Dent Res* 1994;102:68–72.
89. Hildebolt CF, Rupich RC, Vannier MW, et al. Inter-relationships between bone mineral content measures. Dual energy radiography (DER) and bitewing radiographs (BWX). *J Clin Periodontol* 1993;20:739–745.
90. Solar P, Ulm CW, Thornton B, Matejka M. Sex-related differences in the bone mineral density of atrophic mandibles. *J Prosthet Dent* 1994;71:345–349.
91. Ulm CW, Solar P, Ulm MR, Matejka M. Sex-related changes in the bone mineral content of atrophic mandibles. *Calcif Tissue Int* 1994;54:203–207.
92. Zubery Y, Dove SB, Ebersole J. An in vitro study of the characteristics of a computer-aided radiographic evaluation (CARE) system for longitudinal assessment of density changes. *J Periodont Res* 1993;28:233–240.
93. Devlin H, Horner K. Measurement of mandibular bone mineral content using the dental panoramic tomogram. *J Dent* 1991;19: 116–120.
94. Horner K, Devlin H. Clinical bone densitometric study of mandibular atrophy using dental panoramic tomography. *J Dent* 1992;20: 33–37.
95. Jeffcoat MK, Reddy MS. Digital subtraction radiography for longitudinal assessment of peri-implant bone change: Methods and validation. *Adv Dent Res* 1993;7:196–201.
96. Corten FG, van't Hof MA, Buijs WC, Hoppenbrouwers P, Kalk W, Corstens FH. Measurement of mandibular bone density ex vivo and in vivo by dual-energy X-ray absorptiometry. *Arch Oral Biol* 1993;38:215–219.
97. Krall EA, Dawson-Hughes B, Papas A, Garcia RI. Tooth loss and skeletal bone density in healthy post-menopausal women. *Osteoporos Int* 1994;4:104–109.
98. Daniell H. Postmenopausal tooth loss. Contributions to edentulism by osteoporosis and cigarette smoking. *Arch Intern Med* 1983;143: 1678–1682.
99. Lundgren S, Rosenquist JB. Short-term bone healing in calcium deficiency osteopenia and disuse osteopenia: Experimental studies in adult rats. *Scand J Dent Res* 1992;100:337–339.
100. Phillips HB, Ashley FP. The relationship between periodontal disease and a metacarpal bone index. *Br Dent J* 1973;134:237–239.
101. Ward VJ, Manson JD. Alveolar bone loss in periodontal disease and the metacarpal index. *J Periodontol* 1973;44:763–769.
102. von Wowern N, Stoltze K. Comparative bone morphometric analysis of mandibles in second metacarpals. *Scand J Dent Res* 1979;87:358–364.
103. von Wowern N, Hjorting-Hansen E. The mandibular bone mineral content in relation to vestibulolingual sulcoplasty. A 2-year follow-up. *J Prosthet Dent* 1991;65:804–808.
104. Elders PJ, Habets LL, Netelenbos JC, van der Linden LW, van der Stelt PF. The relation between periodontitis and systemic bone mass in women between 46 and 55 years of age. *J Clin Periodontol* 1992;19:492–496.
105. Groen JJ, Menczel J, Shapiro S. Chronic destructive periodontal disease in patients with presenile osteoporosis. *J Periodontol* 1968;39:19–23.
106. Kribbs PJ. Comparison of mandibular bone in normal and osteoporotic women. *J Prosthet Dent* 1990;63:218–222.
107. Machtei EE, Christersson LA, Grossi SG, Dunford R, Zambon JJ, Genco RJ. Clinical criteria for the definition of "established periodontitis." *J Periodontol* 1992;63:206–214.
108. Hausmann E, Allen K, Carpio L, Christersson LA, Clerehugh V. Computerized methodology for detection of alveolar crestal bone loss from serial intraoral radiographs. *J Periodontol* 1992;63:657–662.

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